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Amendment dated July 17, 2003
Preliminary Amendment of July 17, 2003

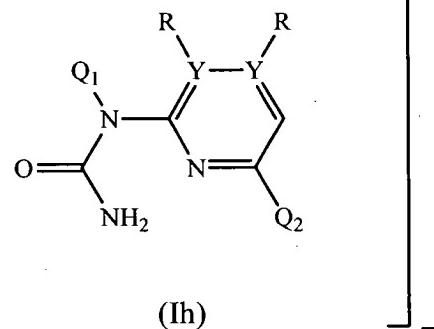
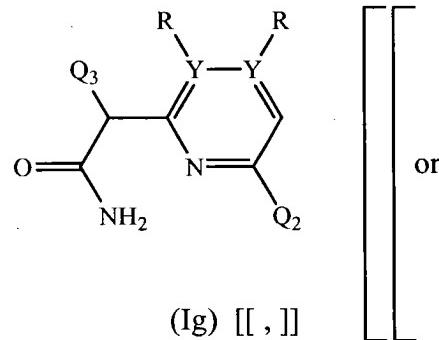
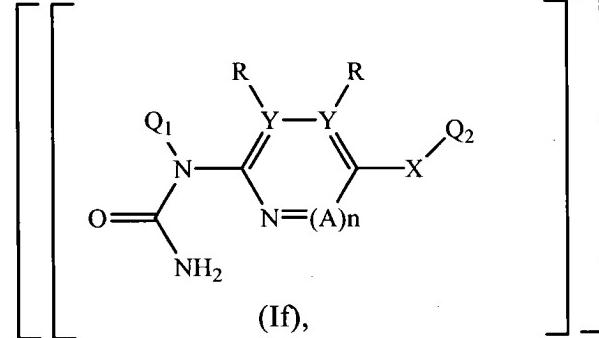
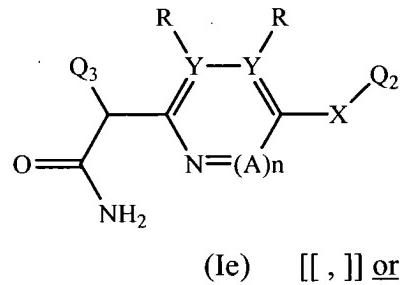
AMENDMENTS TO THE CLAIMS

Claims 1-37 are currently pending. Please cancel claims 1-2, 4-7, 16-17 and 24. Please amend claims 3, 8-9, 11-14, 18, 21-23, and 25-26 as indicated below. This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1-2. (Canceled)

3. (Amended) A compound of the formula:



wherein:

Q_3 is a 5-6 membered aromatic carbocyclic or heterocyclic ring system; or an 8-10 membered bicyclic ring system comprising aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic

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heterocyclic ring; wherein Q₃ is substituted with 1 to 4 substituents, each of which is independently selected from halo; C₁-C₃ alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; [[CONR']] CONHR'; SR'; S(O₂)N(R')₂; SCF₃; CN; N(R')C(O)R⁴; N(R')C(O)OR⁴; N(R')C(O)C(O)R⁴; N(R')S(O₂)R⁴; N(R')R⁴; N(R⁴)₂; OR⁴; OC(O)R⁴; OP(O)₃H₂; or [[N=C-N(R')₂]] N=CH-N(R')₂;

[[A, Q₁, Q₂, R, R', X, Y and n are as defined in claim 1]]

Q₂ is selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems, or 8-10 membered bicyclic ring systems consisting of aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein:

Q₂ is optionally substituted with up to 4 substituents, independently selected from halo, CH=N-OH, or CH=O; C₁-C₃ straight or branched alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, NH-CH₃, NHCH₂CH₂OH, NHCH₂CH(OH)CH₂OH, CH₂OCH₂OCH₃, NHCH₂CH₂NH₂, NH-phenyl, piperazinyl, pyrrolidinyl or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; CONHR'; R³; OR³; NHR³; SR³; C(O)R³; C(O)N(R')R³; C(O)OR³; SR'; S(O₂)N(R')₂; SCF₃; N=CH-N(R')₂; CH=N-OH; CH=O; or CN;

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wherein R' is selected from hydrogen, (C₁-C₃)-alkyl; (C₂-C₃)-alkenyl or alkynyl; phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R³ is selected from a 5-6 membered aromatic carbocyclic or heterocyclic ring system;

R⁴ is (C₁-C₄)-alkyl optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂; or a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂;

X is selected from -S-, -O-, -S(O₂)-, -S(O)-, -S(O₂)-, N(R²)-, -N(R²)-S(O₂)-, -N(R²)-C(O)O-, -O-C(O)-N(R²), -C(O)-, -C(O)O-, -O-C(O)-, -C(O)-N(R²)-, -N(R²)-C(O)-, -N(R²)-, -C(R²)₂-, -C(OR²)₂-, -CH(OH)-;

each R is independently selected from hydrogen, -R², -N(R²)₂, -OR², SR², -C(O)-N(R²)₂, -S(O₂)-N(R²)₂, or -C(O)-OR², wherein two adjacent R are optionally bound to one another and, together with each carbon to which they are respectively bound, form a 4-8 membered carbocyclic or heterocyclic ring;

R² is selected from hydrogen, (C₁-C₃)-alkyl, or (C₁-C₃)-alkenyl; each optionally substituted with -N(R')₂, -OR', SR', -C(O)-N(R')₂, -S(O₂)-N(R')₂, -C(O)-OR', or R³.

Y is selected from C or N;

A, if present, is selected from N or CR'; and

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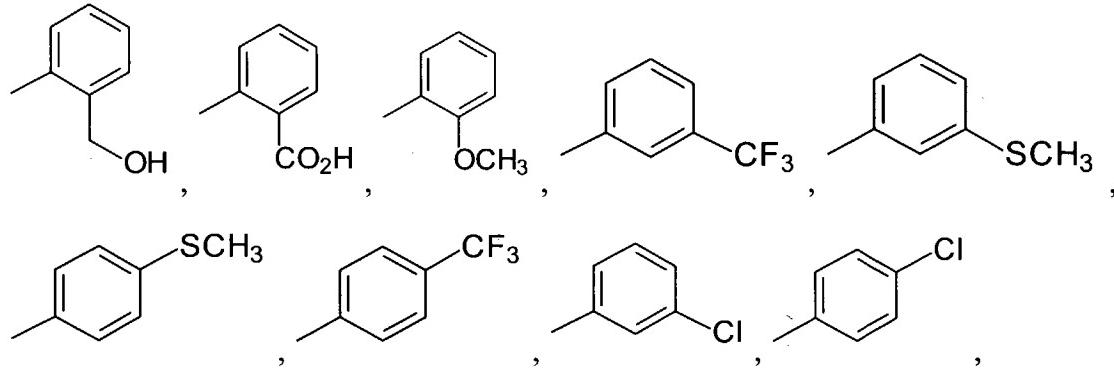
n is 0 or 1;

provided that when a compound is of formula Ig, Q₃ is 2,6-dichlorophenyl and both R substituents are H, then Q₂ is neither phenyl nor p-fluorophenyl; and when a compound is of formula Ie, and Q₃ is 2,6-dichlorophenyl, both R substituents are H, and X is S, then Q₂ is not phenyl.

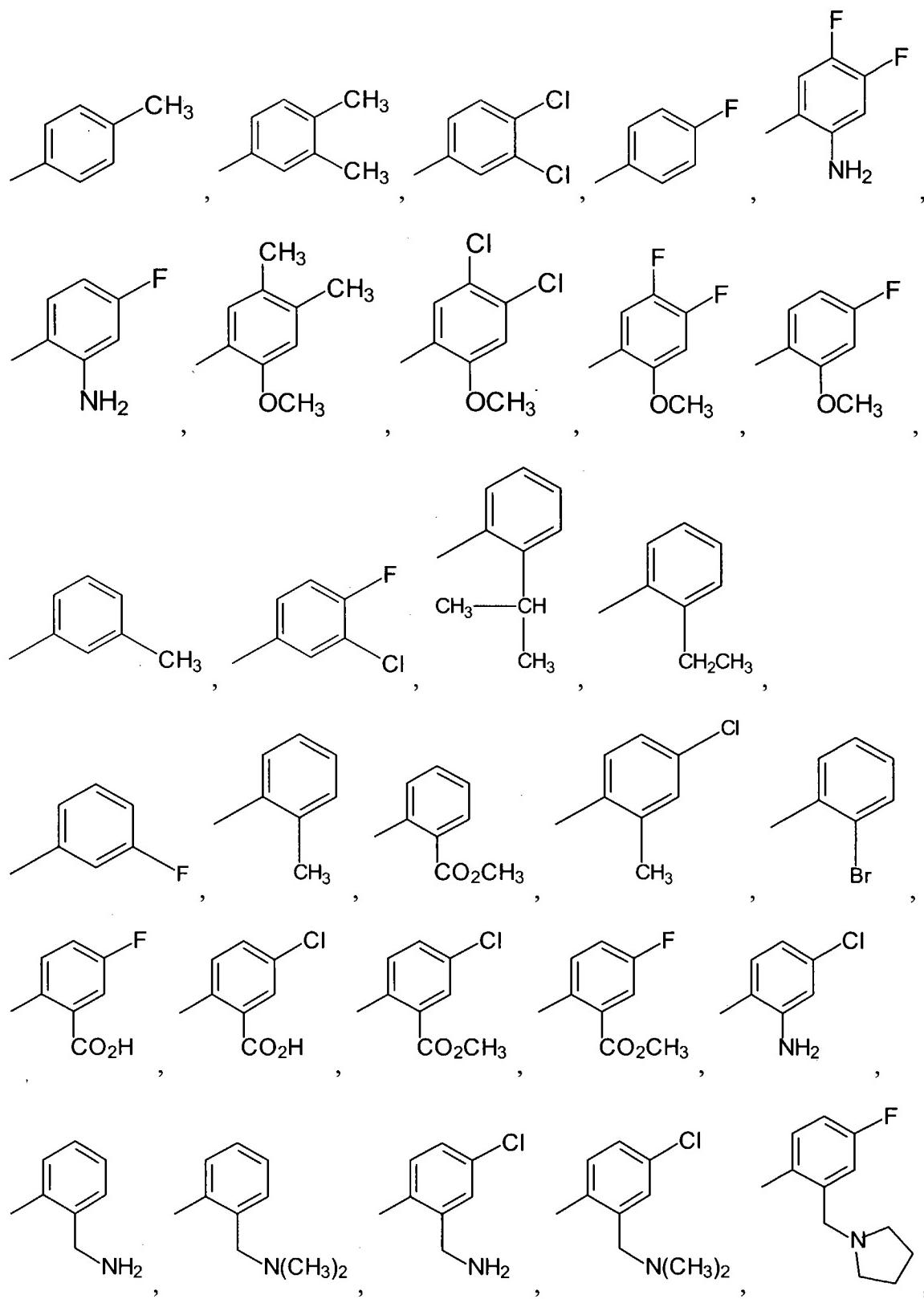
4-7. (Cancelled)

8. (Currently Amended) The compound according to [[any one of claims]] claim [[1-3]] 3, wherein Q₂ is selected from phenyl or pyridyl and wherein Q₂ optionally contains up to 3 substituents, each of which is independently selected from chloro, fluoro, bromo, methyl, ethyl, isopropyl, -OCH₃, -OH, -NH₂, -CF₃, -OCF₃, -SCH₃, -OCH₃, -C(O)OH, -C(O)OCH₃, -CH₂NH₂, -N(CH₃)₂, -CH₂-pyrrolidine and -CH₂OH.

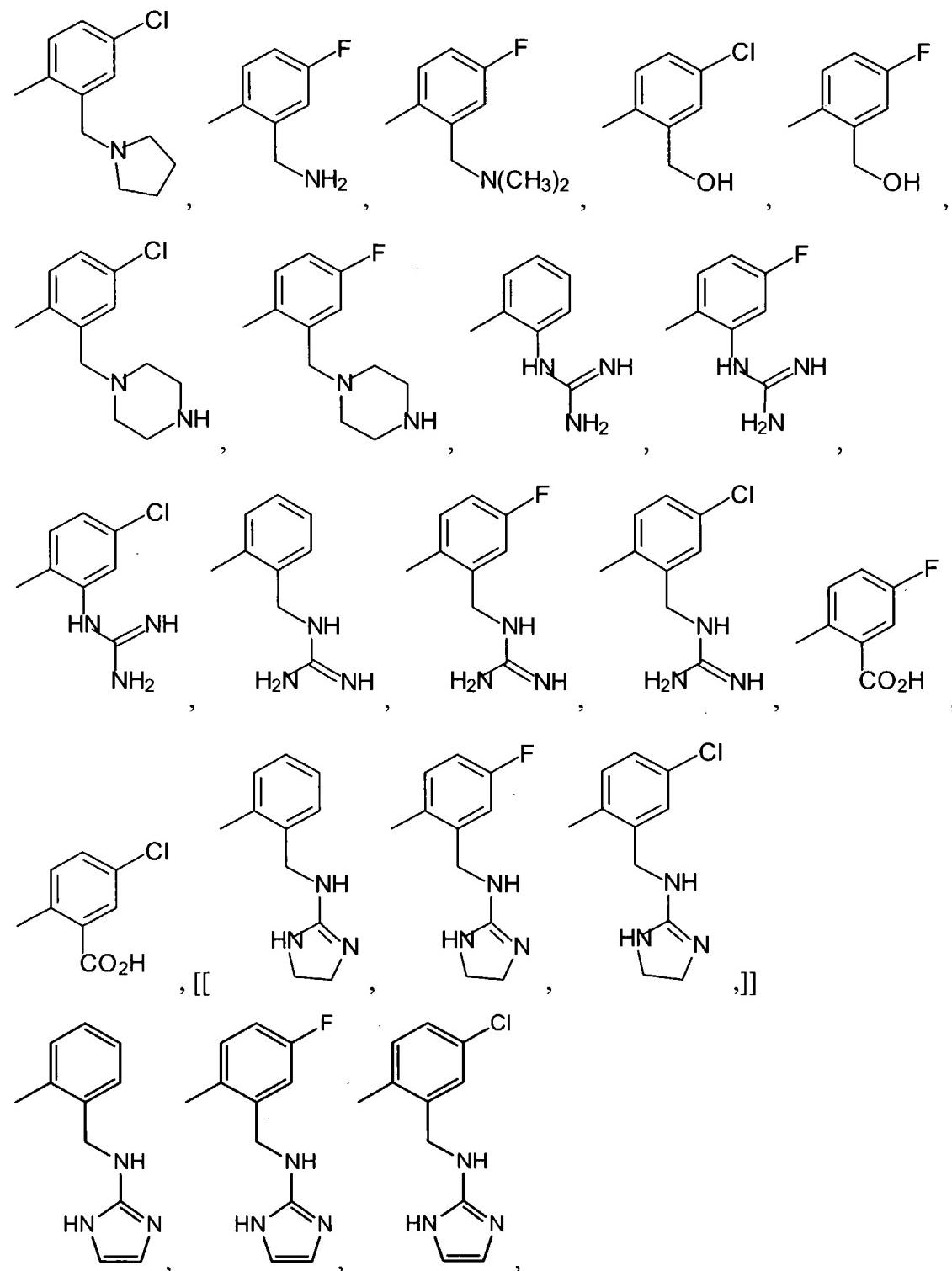
9. (Currently Amended) The compound according to claim 8, wherein, Q₂ is selected from:



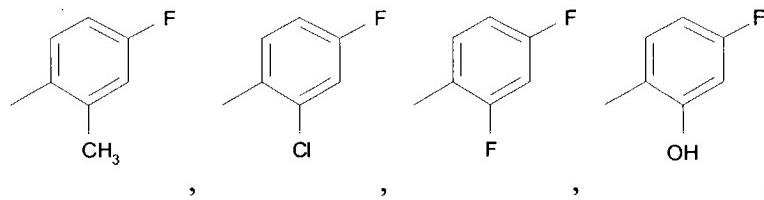
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, , , ,
unsubstituted 2-pyridyl or unsubstituted phenyl.

10. (Original) The compound according to claim 9, wherein Q₂ is selected from phenyl, 2-isopropylphenyl, 3,4-dimethylphenyl, 2-ethylphenyl, 3-fluorophenyl, 2-methylphenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 2-carbomethoxyphenyl, 2-carboxyphenyl, 2-methyl-4-chlorophenyl, 2-bromophenyl, 2-pyridyl, 2-methylenehydroxyphenyl, 4-fluorophenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2,4-difluorophenyl, 2-hydroxy-4-fluorophenyl or 2-methylenehydroxy-4-fluorophenyl.

11. (Currently Amended) The compound according to [[any one of claims]] claim [[1-3]] 3, wherein X is selected from -S-, -O-, -S(O₂)-, -S(O)-, -N(R²)-, -C(R²)- or -C(O)-.

12. (Currently Amended) The compound according to claim [[10]] 11, wherein X is S.

13. (Currently Amended) The compound according to [[any one of claims 1 to]] claim 3, wherein n is 1 and A is N.

14. (Currently Amended) The compound according to [[any one of claims 1 to]] claim 3, wherein each Y is C.

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15. (Original) The compound according to claim 14, wherein each R attached to Y is independently selected from hydrogen or methyl.

16-17. (Canceled)

18. (Currently Amended) The compound according to claim 3, wherein Q₃ is substituted with 2 to 4 substituents, wherein at least one of said substituents is present in the ortho position relative to the point of attachment of Q₃ to the rest of the inhibitor.

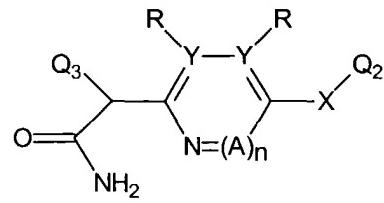
19. (Original) The compound according to claim 18, wherein both ortho positions are occupied by one of said independently selected substituents.

20. (Original) The compound according to claim 19, wherein Q₃ is a monocyclic carbocyclic ring; and each of said ortho substituents on Q₃ are independently selected from halo or methyl.

21. (Currently Amended) The compound according to claim 19, wherein Q₃ contains 1 to 2 substituents in addition to said ortho substituents, said additional substituents being independently selected from NR'₂, OR', CO₂R', CN, N(R')C(O)R⁴; N(R')C(O)OR⁴; N(R')C(O)C(O)R⁴; N(R')S(O)₂R⁴; N(R')R⁴; N(R⁴)₂; OR⁴; OC(O)R⁴; OP(O)₃H₂; or [[N=C-N(R')₂]] N=CH-N(R')₂.

22. (Currently Amended) The compound according to claim 3, wherein said compound is a compound of formula Ie:

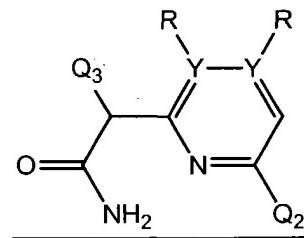
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and is selected from any one of [[compounds 201 or 203 to 209, set forth in Table 3]] the following compounds:

<u>cpd #</u>	<u>structure</u>	<u>cpd #</u>	<u>structure</u>
208		209	

23. (Currently Amended) The compound according to claim 3, wherein said compound is a compound of formula Ig:



and is selected from any one of [[compounds 202/301, 302 to 399, or 1301, set forth in Table 4]] the following compounds:

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cpd #	Structure	cpd #	structure
<u>302</u>		<u>310</u>	
<u>303</u>		<u>311</u>	
<u>304</u>		<u>312</u>	
<u>305</u>		<u>313</u>	

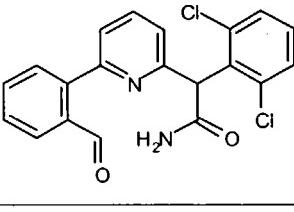
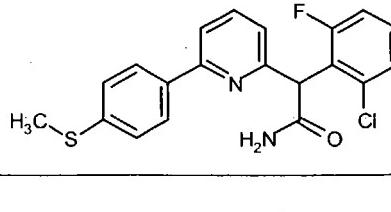
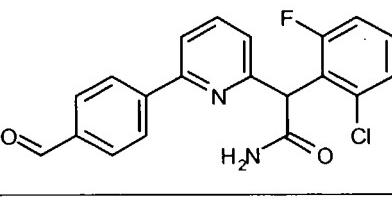
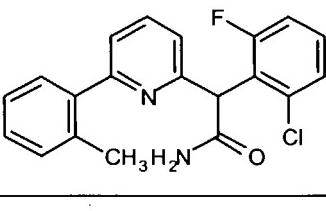
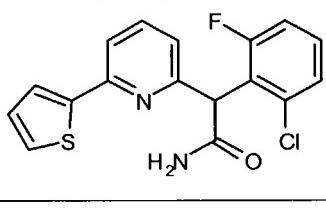
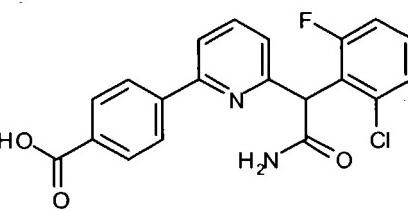
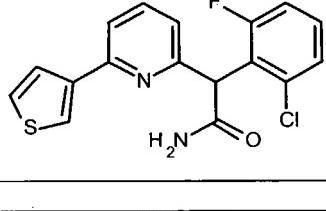
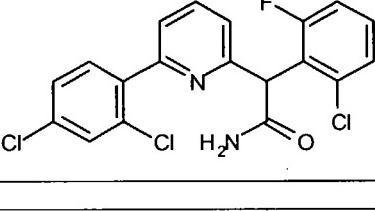
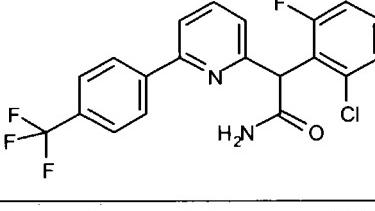
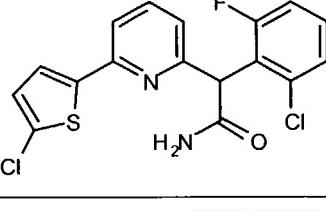
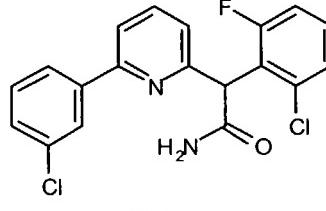
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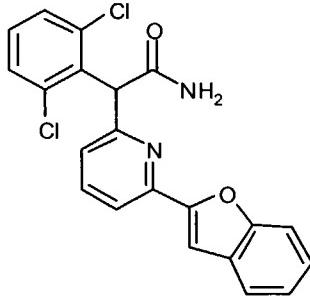
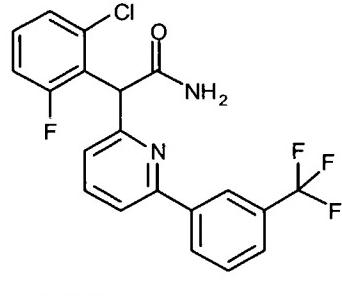
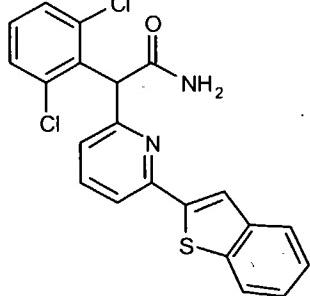
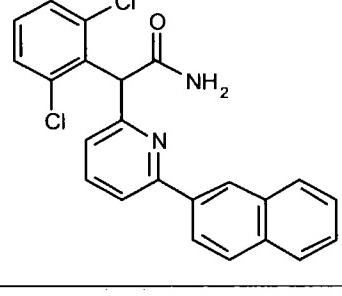
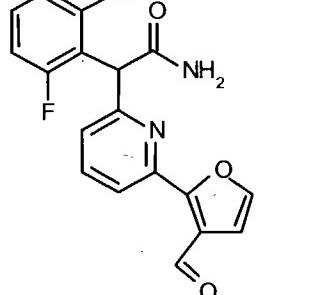
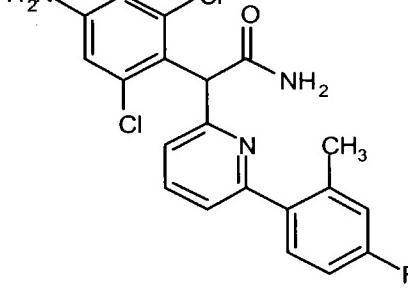
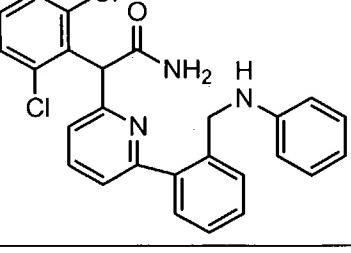
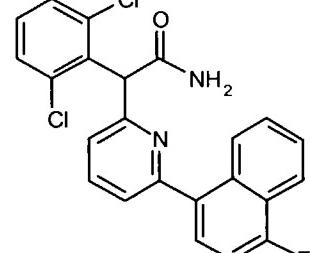
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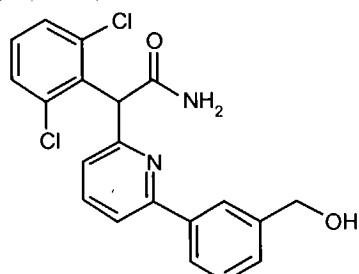
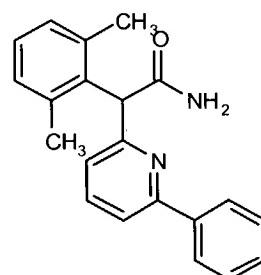
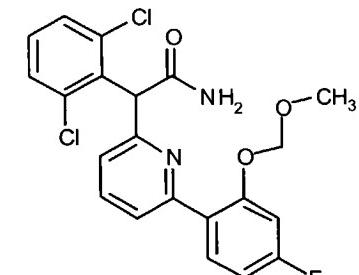
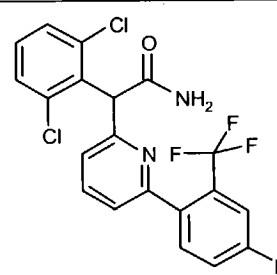
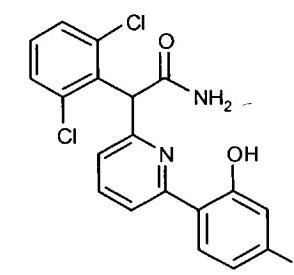
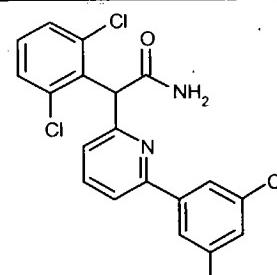
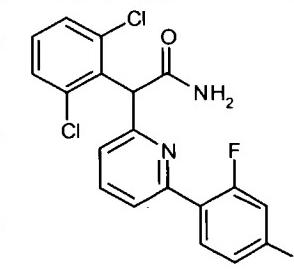
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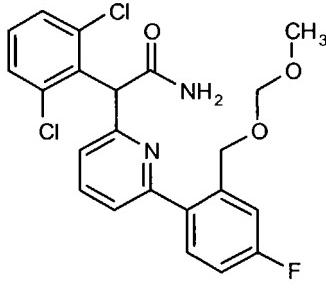
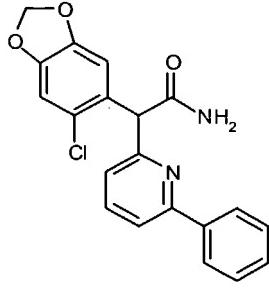
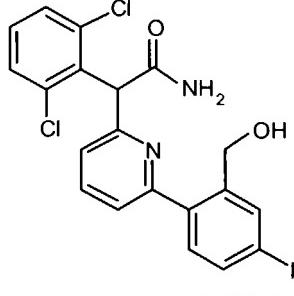
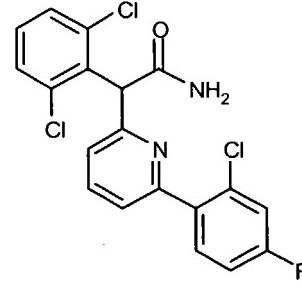
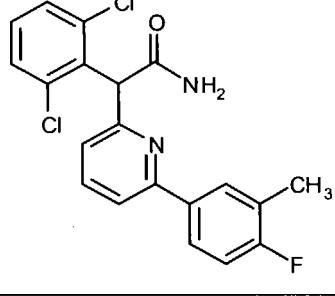
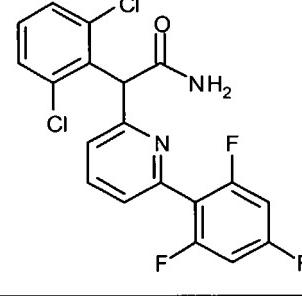
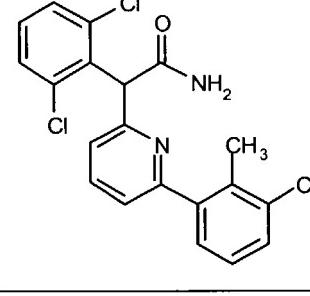
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24. (Canceled)

25. (Currently Amended) A pharmaceutical composition comprising an amount of a compound according to [[any one of claims 1 to]] claim 3 effective to inhibit p38, and a pharmaceutically acceptable carrier.

26. (Currently Amended) A method of treating or preventing inflammatory diseases, autoimmune diseases, viral diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke or myocardial ischemia, renal ischemia, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxide synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 25.

27. (Original) The method according to claim 26, wherein said use is to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

28. (Original) The method according to claim 26, wherein said use is to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

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29. (Original) The method according to claim 26, wherein said use is to treat or prevent a destructive bone disorder selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.
30. (Original) The method according to claim 26, wherein said use is to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.
31. (Original) The method according to claim 26, wherein said use is to treat or prevent an infectious disease selected from sepsis, septic shock, or Shigellosis.
32. (Original) The method according to claim 26, wherein said use is to treat or prevent a viral disease selected from acute hepatitis infection, HIV infection or CMV retinitis.
33. (Original) The method according to claim 26, wherein said use is to treat or prevent a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury.
34. (Original) The method according to claim 26, wherein said use is to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.
35. (Original) The method according to claim 26, wherein said use is to treat or prevent a condition associated with prostaglandin endoperoxide synthase-2 selected from edema, fever, analgesia or pain.

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36. (Original) The method according to claim 35, wherein said pain is selected from neuromuscular pain, headache, cancer pain, dental pain or arthritis pain.
37. (Original) The method according to claim 26, wherein said use is to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.